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REVIEW ARTICLE

Transcranial magnetic stimulation in sport science: A commentary

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Abstract

The aim of this commentary is to provide a brief overview of transcranial magnetic stimulation (TMS) and highlight how this technique can be used to investigate the acute and chronic responses of the central nervous system to exercise. We characterise the neuromuscular responses to TMS and discuss how these measures can be used to investigate the mechanisms of fatigue in response to locomotor exercise. We also discuss how TMS might be used to study the corticospinal adaptations to resistance exercise training, with particular emphasis on the responses to shortening/lengthening contractions and contralateral training. The limited data to date suggest that TMS is a valuable technique for exploring the mechanisms of central fatigue and neural adaptation.

Keywords: *Contralateral adaptation, eccentric training, exercise, fatigue, TMS, recovery*

Introduction

Early in the nineteenth century, Faraday observed that a changing magnetic field produces an electric current. In 1982, Polson, Barker, and Freeston produced the first magnetic stimulator capable of peripheral nerve stimulation, and in 1985, Barker, Jalinous, and Freeston were the first to describe magnetic stimulation of the human motor cortex. These observations led to the development of transcranial magnetic stimulation (TMS). With TMS, a rapidly changing magnetic field delivered via a coil held over the scalp induces weak electrical currents that excite underlying neural tissue. These currents cause activity in specific parts of the brain, with minimal discomfort, allowing neural functions and interconnections to be studied in the intact human. The ability of TMS to stimulate deep neural structures, such as the motor cortex, has enabled researchers to investigate the integrity of the brain to muscle pathway and the functionality of cortical networks. To appreciate the potential of TMS, it is necessary to characterise the neuromuscular responses to cortical stimulation. Since neurons con-

necting to muscles in distinct regions of the body have their own geographical location across the motor cortex [known as the motor homunculus (Penfield & Boldrey, 1937)], it is possible to deliver magnetic stimuli to discrete collections of neurons relating to specific muscle groups (Figure 1).

Transcranial magnetic stimulation has been used to study the human nervous system within clinical populations (Hallett, 1996; Hallett & Rothwell, 2011; Rothwell, 2011); mechanisms of fatigue in small, isolated muscle groups (Gandevia, 2001; Taylor & Gandevia, 2001, 2008); corticospinal contributions during human gait (Barthelemy & Nielsen, 2010; Capaday, Lavoie, Barbeau, Schneider & Bonnard, 1999) and acute neural adaptations following strength training (Carroll, Riek, & Carson, 2001; Gruber, Linnamo, Strojnik, Rantalainen, & Avela, 2009; Jensen, Marstrand, & Nielsen, 2005). However, only a limited number of studies have used TMS to investigate cortical function of involved muscles after locomotor exercise. Specifically, responses to TMS have been obtained in the tibialis anterior after marathon running (Ross, Middleton,

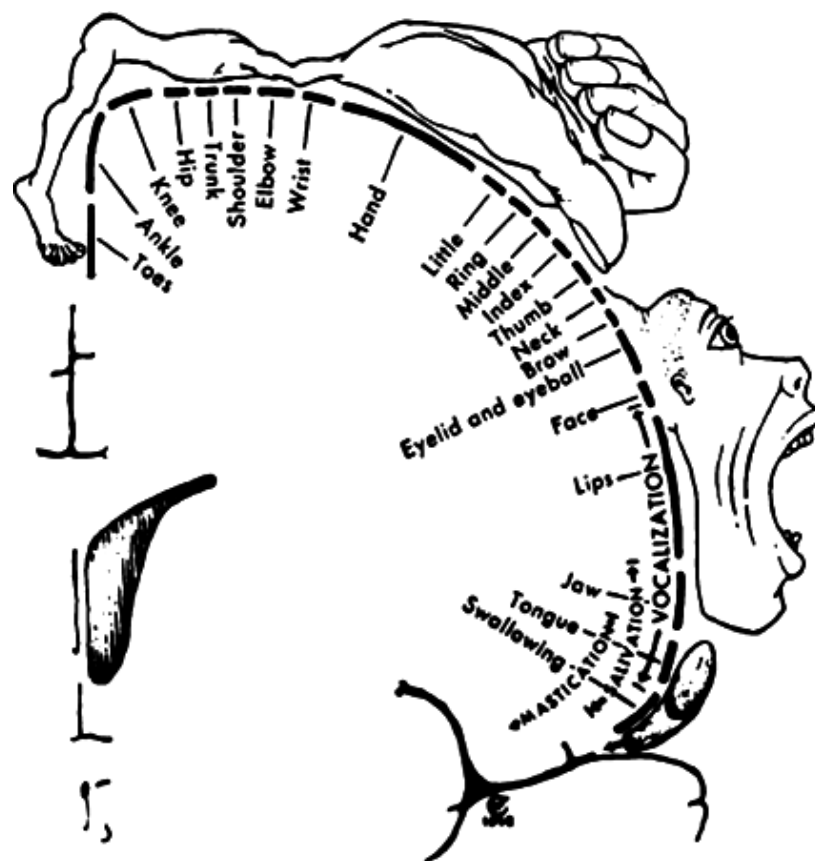


Figure 1. The first mapping of the human motor homunculus. Reprinted from Penfield & Rasmussen (1950), with permission.

Shave, George, & Nowicky, 2007) and cycling (Sidhu, Hoffman, Cresswell, & Carroll, 2012); the knee extensors (Goodall, Gonzalez-Alonso, Ali, Ross, & Romer, 2012; Hollge et al., 1997; Ross, Gregson, Williams, Robertson, & George, 2010; Sidhu, Bentley, & Carroll, 2009b) and the diaphragm (Verin et al., 2004). The remainder of this section provides evidence-based physiological and methodological considerations for the measurement of parameters evoked by TMS, including motor evoked potentials (MEPs), cortical silent period (CSP) and cortical voluntary activation.

Motor evoked potential

An MEP is an electrical potential that can be recorded from a muscle following direct stimulation of the motor cortex using TMS. The characteristics of an MEP can be monitored to reveal changes in corticospinal excitability (Mills, 1999). TMS-induced MEPs can be elicited in a target muscle only above a given stimulation intensity, termed the resting motor threshold (rMT). This threshold has been defined as the minimum stimulation intensity needed to elicit an MEP of at least 50 μ V with 50% probability (e.g. 5 out of 10 stimuli) in a fully relaxed

muscle (Rossini et al., 1994) and is different between individuals and different muscle groups. To ensure the same relative intensity of stimulation across all participants in a particular investigation, it is common for the stimulation intensity to be set at 120–130% of the intensity that elicits rMT. Thus, the rMT has been termed the ‘basic unit of dosing’ in TMS experiments (Borckardt, Nahas, Koola, & George, 2006). Ultimately, descending drive evoked via cortical stimulation (and thus the size of the MEP response) depends on the stimulus intensity, the excitability of cortical neurons and the excitability of the motoneuron pool (Taylor & Gandevia, 2001). Characteristics of an MEP are shown in Figure 2. The MEP latency is a measure of central motor conduction time – the velocity at which the neural signal is propagated from the motor cortex to the muscle. The MEP amplitude provides a measure of the magnitude of corticospinal excitability. The MEP area, when compared to the area of the maximal electromyography (EMG) response evoked using motor nerve stimulation, reveals the proportion of the motor unit pool recruited by TMS.

During a voluntary contraction, corticospinal neurons and motoneurons become more excitable. Consequently, TMS of the same intensity evokes a

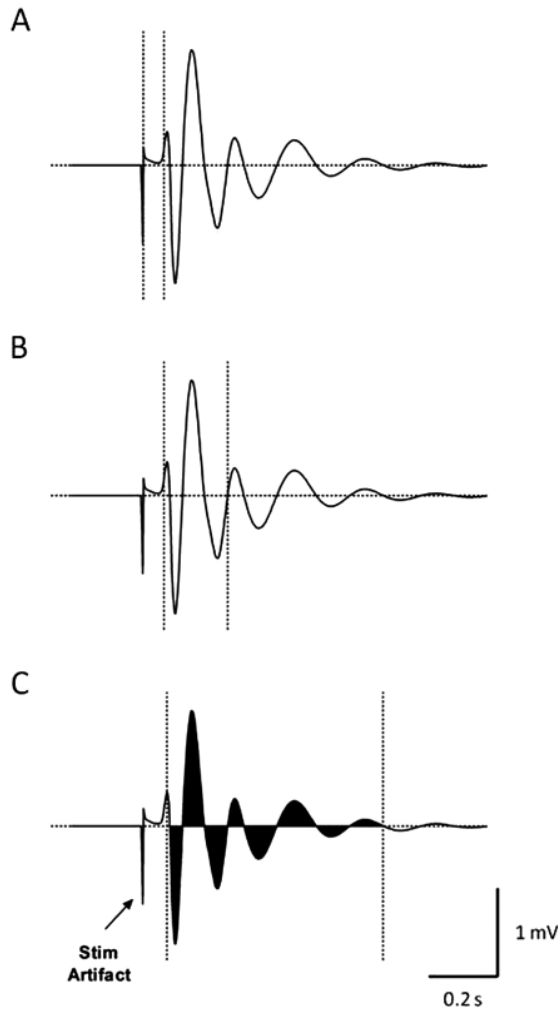


Figure 2. Representative biphasic motor evoked potential (MEP) recorded from the vastus lateralis in response to single pulse stimulation of the motor cortex. Dashed vertical lines represent where cursors are placed to measure the evoked response. *A*, measurement of latency; *B*, measurement of peak-to-peak amplitude; and *C*, measurement of area.

much larger MEP in contracting muscle than during rest (Hess, Mills, & Murray, 1987; Rothwell, Thompson, Day, Boyd, & Marsden, 1991). The size of the MEP evoked by TMS increases with the strength of brief isometric contractions, with the largest MEP commonly evoked during a contraction at about 50% of maximal voluntary contraction (MVC), suggesting that at this level of contraction most motoneurons are activated. Further increases in contraction intensity (>50% MVC) tend to show a plateau in MEP amplitude and area in several human muscle groups, including the elbow flexors (Todd, Taylor, & Gandevia, 2003, 2004), wrist extensors (Lee, Gandevia, & Carroll, 2008) and knee extensors (Goodall, Romer, & Ross, 2009; Sidhu, Bentley, & Carroll, 2009a). Similar MEP amplitudes evoked during contractions of

50–100% MVC suggest that the cortical stimulus activates a comparable proportion of motoneurons; however, this is not the case for stimulations delivered during weaker contractions (<50% MVC). The plateau in MEP amplitude at higher forces is the result of a decline in motoneuron output in response to the stimulus, arising from an inability of some motoneurons to fire in response to the excitatory input (Todd et al., 2003). In turn, the plateau in MEP area at higher forces is due to an inability of the cortical stimulus to excite the firing motoneuron when it arrives at the beginning of its recovery cycle (Matthews, 1999).

Cortical silent period

If a strong TMS stimulus is delivered during an intense voluntary contraction, a period of EMG ‘silence’ (typically lasting >200 ms) will follow the MEP (Taylor & Gandevia, 2001). The mechanisms of this CSP are not completely understood, but it is generally accepted that the initial and later parts are of spinal and cortical origin, respectively (Chen, Lozano, & Ashby, 1999; Fuhr, Agostino, & Hallett, 1991; Inghilleri, Berardelli, Cruccu, & Manfredi, 1993; Taylor & Gandevia, 2001). The CSP is quantified from the point of stimulation to the resumption of ongoing EMG. Whilst some investigators have used visual inspection to identify the resumption of ongoing EMG (Sidhu et al., 2009b; Todd, Butler, Taylor, & Gandevia, 2005), this method can lead to inaccuracies (Daskalakis et al., 2003; Fritz, Braune, Pylatiuk, & Pohl, 1997). Others have used more robust procedures based upon mathematical modelling (Damron, Dearth, Hoffman, & Clark, 2008; King, Kuppuswamy, Strutton, & Davey, 2006).

Cortical voluntary activation

Maximal voluntary activation is the extent to which a muscle is activated by the central nervous system (CNS) during a MVC. Traditionally, voluntary activation has been assessed using the interpolated twitch technique (Merton, 1954). Briefly, this technique involves delivering a supramaximal stimulus to the motor nerve during maximal contraction and assuming that any additional force evoked by the stimulus represents a deficit in complete activation of the muscle. This method allows researchers to monitor CNS function and provides an opportunity to investigate the mechanisms of exercise-induced fatigue. The twitch interpolation method is limited, however, because the exact site of failure within the CNS cannot be discerned. If the superimposed twitch (SIT) increases and central fatigue is evident, failure of drive may occur at

any point or combination of points proximal to the point of stimulation (i.e. spinal, sub-cortical or cortical).

More recently, maximal voluntary activation has been assessed using TMS in order to further localise the site of impaired neural drive to the target muscle (Todd et al., 2003, 2004). The presence of a SIT produced by TMS during a maximal contraction implies that motor cortical output is suboptimal and insufficient to activate all motor units to produce maximal force. Gandevia, Allen, Butler, and Taylor (1996) identified an increase in the SIT elicited by motor cortical stimulation as 'supraspinal fatigue' (a subcomponent of central fatigue), whereby any impairment in neural drive is situated at or above the level of motor cortical output. However, the measurement of cortical voluntary activation is less straightforward than the traditional twitch interpolation technique. First, the resting twitch, which is needed for the calculation of voluntary activation, has to be estimated by extrapolating the negative linear relationship between voluntary force (between 50 and 100% MVC) and SIT amplitude (Figure 3). Estimation of the resting twitch is necessary because corticospinal excitability is lower at rest than during activity (Rothwell et al., 1991), such that during rest a cortical stimulus activates fewer motoneurons and provides a non-facilitated stimulus within the target muscle. In addition, it is important that the muscle

of interest is stronger and more easily excited by TMS than its antagonist as TMS can activate surrounding muscles as well as the muscle of interest, thereby invalidating the measurement of cortical voluntary activation (Lee et al., 2008; Todd et al., 2003, 2004).

Cortical voluntary activation has been measured in only a small number of muscles, as the neuromuscular characteristics of some muscles are not deemed suitable for the technique (i.e. where an antagonist muscle group is of similar strength to that of the agonist muscle group causing co-activation during motor cortical stimulation). Cortical voluntary activation and supraspinal fatigue were first measured in the elbow flexors (Todd et al., 2003, 2004). Recently, the TMS voluntary activation technique has been validated for the wrist extensors (Lee et al., 2008) and back extensors (Lagan, Lang, & Strutton, 2008). However, none of these muscle groups lend themselves well to the study of dynamic locomotor exercise. More recently, TMS has been validated for the knee extensors (Goodall et al., 2009; Sidhu et al., 2009a) – a muscle group important for locomotion during cycling and running. The next section discusses how the mechanical and electromyographic responses to TMS can be used to understand the mechanistic basis of fatigue following locomotor exercise.

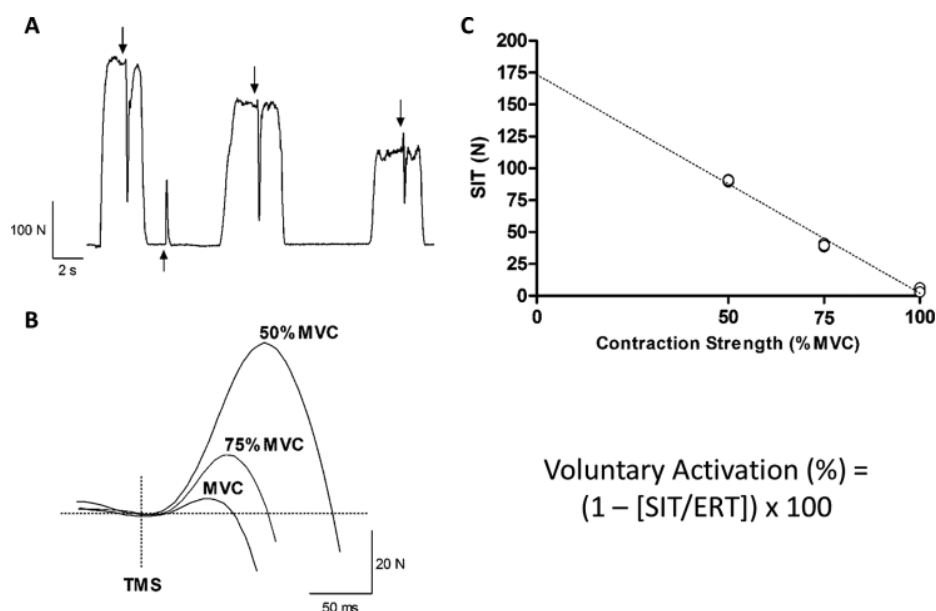


Figure 3. *A*, representative force trace illustrating three levels of voluntary knee-extension during a typical measurement of cortical voluntary activation. Transcranial magnetic stimulation (TMS) was delivered over the left motor cortex during 100, 75 and 50% maximal voluntary contraction (MVC). Downward arrows indicate the timing of TMS and the upward arrow indicates timing of an electrical stimulus delivered to the femoral nerve. *B*, raw force traces from the same participant showing the superimposed twitch (SIT) responses to TMS at 100, 75 and 50% MVC used for the subsequent determination of the estimated resting twitch (ERT; *C*) and hence cortical voluntary activation. Background forces in *B* have been offset to allow direct comparison between contractions. Redrawn from Goodall, Ross, and Romer (2010), with permission.

Motor cortical responses following locomotor exercise

Hollge et al. (1997) were the first to apply TMS to the study of dynamic exercise. Those authors found significant decreases in MEP amplitude evoked in the primary muscles associated with exhaustive 400 m running, press-ups and dumbbell holding. The decreases in MEP amplitude were described as *central* failure because responses to peripheral nerve stimulation were unchanged (Hollge et al., 1997). Confirming this CNS impairment, reduced intracortical facilitation (measured using a paired pulse technique, discussed later) was found after pull-ups to task failure, reflecting a decreased excitability of interneuronal circuits within the motor cortex (Tergau et al., 2000). Verin et al. (2004) demonstrated reduced MEP amplitudes of both the quadriceps and diaphragm after maximal incremental treadmill exercise, with no change in the response to peripheral nerve stimulation (i.e. muscle contractility and excitability). The depression of MEP amplitude was larger for the diaphragm compared to the quadriceps, highlighting that the corticospinal pathways of different muscle groups may be affected differently during fatigue. Ross et al. (2007) demonstrated that motor cortex excitability to the tibialis anterior decreased after a treadmill marathon and contributed to a loss in force generating capacity. A global effect was discounted based on a lack of decrease in maximal strength of a muscle group not used during the activity; thus, the excitability changes appeared to be specific to 'involved' muscles. Furthermore, in a study where well-trained cyclists completed 20 prolonged cycling bouts over 23 days, Ross et al. (2010) noted an enduring impairment of force generating capacity and corticospinal excitability (MEP amplitude) of the quadriceps that was evident even after 18 h of recovery. Findings from this latter study suggest that central fatigue is not always a transient phenomenon and that cortical mechanisms may contribute to manifestations of 'overreaching'.

Transcranial magnetic stimulation has also been used to assess supraspinal fatigue of small muscle groups working in isolation. However, we are aware of only two studies that have used this technique to quantify supraspinal fatigue of involved muscles after locomotor exercise. Sidhu et al. (2009b) used TMS to study responses from the knee-extensor muscles after fatiguing bouts of intermittent cycling. The 8 × 5 min bouts of cycling at 80% peak power induced significant drops in cortical voluntary activation (i.e. supraspinal fatigue) that persisted for 45 min post-exercise. These changes were not accompanied by alterations in MEP characteristics, suggesting that the responsiveness of neurons in the pathway from motor cortex to muscle output was

unaffected by this type of activity (Sidhu et al., 2009b). Recently, Goodall et al. (2012) used TMS to evaluate supraspinal fatigue of the knee-extensor muscles in response to sustained, high-intensity cycling in normoxia and acute severe hypoxia. Cortical voluntary activation declined after exercise in both conditions, but the decline was two-fold greater in hypoxia. Collectively, these findings suggest that TMS has the potential to quantify the contribution of central processes to fatigue of limb locomotor muscles.

Motor cortical plasticity in response to resistance exercise

Transcranial magnetic stimulation can be used to investigate physiological states other than fatigue. For example, it is well established that neuromuscular adaptation readily occurs as a result of resistance exercise training (Aagaard et al., 2001; Aagaard, Simonsen, Andersen, Magnusson, & Dyhre-Poulsen, 2002; Hortobagyi, Hill et al., 1996; Sale, 1988). Morphological changes can be ascertained by direct measurements from tissue (e.g. histological staining, fMRI and CT scanning), but such changes cannot readily explain the acute responses to motor tasks and resistance exercise that are almost certainly neurally derived during these early stages of training (Gabriel, Kamen, & Frost, 2006; Sale, 1988). Whilst tools such as EMG offer some indication of electrical activity at the muscle, voluntary contraction is clearly influenced by input from the corticospinal tract. Peripheral motor nerve stimulation can be used to investigate the inhibitory mechanisms of Ia afferent interneurons at the spinal level, using established measures such as the H-reflex (Aagaard et al., 2002). Using one measure in isolation, however, does not provide a complete picture of the complex interaction between the central and peripheral nervous systems (Carroll, Selvanayagam, Riek, & Semmler, 2011).

The primary motor cortex (M1) is heavily involved in voluntary contraction of skeletal muscle and shows a high degree of plasticity, or capacity to change quickly, with motor practice (Jensen et al., 2005; Lee, Hinder, Gandevia, & Carroll, 2010; Selvanayagam, Riek, & Carroll, 2011). In a classic example, Muellbacher et al. (2002) showed that 20 min practice of a ballistic pinching task elicited a significant improvement in task performance. The improvement in task performance was accompanied by an immediate increase in the corticospinal response (MEP), demonstrating that M1 has an adaptive role in the consolidation of motor tasks. Therefore, TMS enables a greater understanding of the behaviour of the corticospinal tract in 'top-down' paradigms, where the effect of motor skills on

corticospinal plasticity and neuromuscular adaptation can be examined. The remainder of this section will explore some potential applications of TMS for the investigation of M1 plasticity during and following different experimental paradigms, including task-specific contractions and resistance exercise training.

Lengthening and shortening contractions elicit different EMG responses (Duchateau & Enoka, 2008; Duchateau, Semmler, & Enoka, 2006; Enoka, 1996; Nardone, Romano, & Schieppati, 1989; Pasquet, Carpentier, & Duchateau, 2006). Specifically, the EMG activity per unit of force is lower during lengthening conditions (Duchateau & Enoka, 2008). Moreover, lengthening contractions show a greater degree of plasticity. For example, the adaptive response is greater for lengthening than shortening contractions (Hortobagyi, Barrier *et al.*, 1996; Hortobagyi, Hill *et al.*, 1996). Lengthening contractions also require less neural activation and have a lower metabolic cost per unit of torque (Bigland-Ritchie & Woods, 1976), along with a lower cardiovascular strain (Overend, Versteegh, Thompson, Birmingham, & Vandervoort, 2000). Thus, lengthening contractions are appealing for many populations beyond athletes, such as the elderly and those with compromised cardiorespiratory function. It has been assumed, to a large extent, that the differences in the neural responses are mediated centrally. Until recently, however, the influence of M1 on the task-specific response to lengthening and shortening contractions was unknown. Magnetic stimulation of M1 can be used to reveal a change in corticospinal excitability depending upon the type and intensity of contraction (Abbruzzese, Morena, Spadavecchia, & Schieppati, 1994; Gruber *et al.*, 2009; Tallent *et al.*, 2012).

By delivering short-interval paired-pulses, it is possible to investigate the potential mechanisms for the aforementioned differences in MEP between contraction types. By varying the inter-stimulus interval, the MEP response can be inhibited or facilitated compared to the response from a single pulse (Figure 4). Paired pulse TMS delivered in



Figure 4. Influence of single and paired pulse transcranial magnetic stimulation (TMS) delivered at rest on the subsequent motor evoked potential (MEP) response. Note how the short interval (2 ms) paired pulse reduces the MEP response, whereas the longer interval (10 ms) paired pulse increases the MEP response. Redrawn from Ni and Chen (2011), with permission.

short intervals of ~ 2 ms will inhibit the corticospinal response (short interval cortical inhibition), whereas longer intervals of ~ 10 ms will facilitate the response (long interval cortical facilitation) (Kujirai *et al.*, 1993). Paired pulses influence a number of neuro-transmitters, including glutamate, dopamine and gamma aminobutyric acid, and the subsequent interaction with task-specific, inhibitory and facilitatory neurons has recently been summarised (Ni & Chen, 2011). Using this approach, it is possible to examine how the MEP response to intracortical inhibition and facilitation may differ between tasks.

The acute MEP responses to muscular contraction are well described. Much of the literature has focused on isometric and ballistic tasks, with far fewer studies incorporating shortening and lengthening contractions. Some studies (Carroll, Riek, & Carson, 2002) have focused on muscles with a high cortical representation of M1 (e.g. first dorsal interosseous and flexor carpi radialis), likely because these muscles are easily accessed with TMS. Fewer studies have examined muscles of the lower limb (Beck *et al.*, 2007; del Olmo, Reimunde, Viana, Acero, & Cudeiro, 2006; Falvo, Sirevaag, Rohrbough, & Earhart, 2010) or large muscles of the upper limb such as biceps brachii (Jensen *et al.*, 2005; Kidgell, Stokes, Castricum, & Pearce, 2010); stimulation of these areas is less straightforward and such experiments present unique challenges, particularly when peripheral stimulation and reflex arcs are also required. Nonetheless, the corticospinal responses in such experimental paradigms show a high degree of plasticity to resistance training and provide an increasing body of evidence that the early increases in strength with resistance training are mediated, at least in part, via cortical mechanisms. Although examination of small distal muscles can characterise the responses and behaviour of M1, it is also important to investigate large muscles of locomotion, the responses of which may differ from those obtained for small muscles. Thus, TMS can be used to explore the mechanistic basis for acute and chronic responses to resistance exercise and motor learning tasks.

Another phenomenon that can be examined using TMS is that of contralateral adaptation (also termed 'cross education'). When carrying out unilateral resistance training, there are increases in strength, physiological cross-sectional area and EMG activity in the involved limb (Hortobagyi, Hill *et al.*, 1996). In addition, there is strong evidence that unilateral resistance training can increase strength and EMG activity in the resting or inactive contralateral homologous muscle (Hortobagyi, Lambert, & Hill, 1997). A recent meta-analysis noted an $\sim 8\%$ increase in strength of the muscle contralateral to the trained

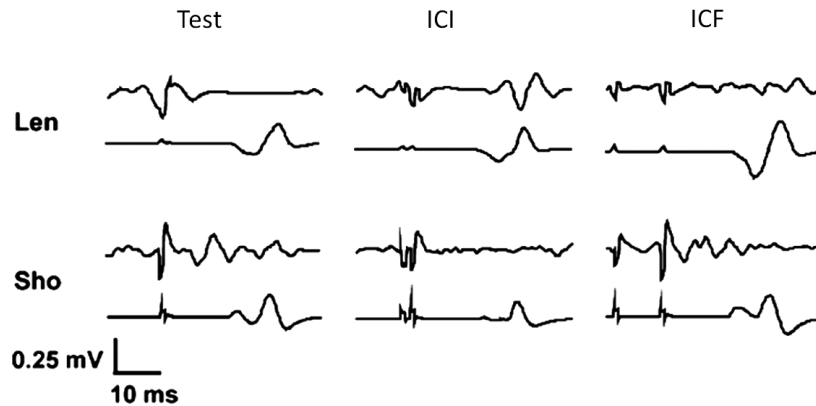


Figure 5. Examples of motor evoked potential (MEP) during lengthening (Len) and shortening (Sho) contractions. The upper EMG traces show the responses in the contracting flexor carpi radialis muscle; the lower traces show the responses in the inactive contralateral homologous muscle. The Test pulse illustrates the MEP response to a single pulse. Paired inhibitory pulses illustrate that the magnitude of intracortical inhibition (ICI) is diminished during Len compared to Test and Sho. Intracortical facilitation (ICF) is increased to a greater extent than both Sho and Test, indicating that corticospinal excitability is greater during lengthening contractions. Reprinted from Howatson et al. (2011), with permission.

one, and this effect was $\sim 52\%$ of the effect for the trained muscle (Carroll, Herbert, Munn, Lee, & Gandevia, 2006). These adaptations are in the absence of changes in physiological cross-sectional area and are thought to stem from changes within the CNS at cortical, sub-cortical and spinal levels (Carroll et al., 2006; Lee & Carroll, 2007). Given the likely contribution of the motor cortices, TMS lends itself well to the investigation of potential mechanisms mediating cross education.

Cross education exhibits a task-specific response, in that the adaptation conferred to the resting contralateral limb is greater for lengthening than shortening contractions. Thus, lengthening contractions appear to be a more powerful stimulus for neuromuscular adaptation in the resting contralateral limb (Hortobagyi et al., 1997). In addition, a single bout of lengthening contractions protects against a subsequent bout of potentially damaging contractions (Howatson & van Someren, 2007). Although these previous investigations speculated that the potential mechanisms were mediated centrally, it was not possible to demonstrate unequivocally the reasons for the observations. In a recent cross-sectional study, however, TMS was used to investigate these contralateral effects by examining the excitability of the resting corticospinal tract during lengthening and shortening contractions (Howatson et al., 2011). There was increased excitability of the M1 ipsilateral to the exercising limb (controlling the contralateral, resting limb). In addition, the magnitude of this corticospinal excitability was greater during lengthening contractions and appeared to be mediated by an attenuation of intracortical and interhemispheric inhibition. Figure 5 shows the differences in MEP amplitude in the resting contralateral limb during lengthening and

shortening contractions of the same intensity; lengthening contractions show less inhibition and greater facilitation than shortening contractions. This information offers a potential mechanism for the increased stimulus for contralateral adaptation noted after lengthening contractions. Such adaptations (cross education) are relevant to individuals with unilateral musculoskeletal injury and immobilisation as well as to post-operative patients and clinical populations such as stroke.

It must be acknowledged that TMS is a tool that provides only an indication of what might be occurring along the corticospinal tract. In isolation, TMS can be used to ascertain additional information of the CNS influence during resistance exercise and other motor tasks. To improve our conceptual understanding, however, we should be mindful of the potential pitfalls and limitations of using a single technique. A combination of techniques incorporated at a segmental level (e.g. the brain stem and spinal cord) enables greater insight into the function of the corticospinal tract and plasticity of the neuromuscular system in response to acute and chronic exercise (Sidhu et al., 2012; Ziemann, 2011). Notwithstanding, TMS is a valuable tool for quantifying the central contributions to exercise-induced fatigue and adaptation.

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